glycogen values fell from a normal of 1.13% to 0.019%. ANTU-poisoned animals were unable to deposit liver glycogen. While these experiments demonstrate a disturbance in carbohydrate metabolism, they do not prove that death from ANTU is due to these changes. In rats large doses of cysteine (1000 mg per kg) afforded protection from death against 10 mg per kg of ANTU. The relation between lung damage and impairment of glycolysis and/or respiration is under investigation.

15240

Modification of Anaphylaxis by Benadryl.*

J. A. WELLS, H. C. MORRIS, AND CARL A. DRAGSTEDT.

From the Department of Pharmacology, Northwestern University Medical School, Chicago, Ill.

It has been recently shown that beta-dimethyl aminoethyl benzhydryl ether hydrochloride (Benadryl) inhibits the action of histamine on the bronchi and ileum of the guinea pig.[1] The subsequent demonstration that this drug is capable of reducing the severity of anaphylaxis in the guinea pig[2] is in accordance with the repeated demonstration that anaphylaxis in the guinea pig is due, in large part, to bronchospasm resulting from the action of histamine which is liberated from the lung.[3-8]

We have demonstrated that Benadryl inhibits the vasodepressor action of histamine in the anesthetized dog and have suggested that this inhibition is due to competition of Benadryl with histamine for its site of action.[9,10] The purpose of the present investigation was to determine the effect of Benadryl against anaphylaxis in the dog, a condition which, as in the guinea pig, is intimately connected with the release and action of histamine.[11-15]

It has been shown that in fatal anaphylaxis in the dog from 3.2 to 4.7 mg of histamine per kilo (measured as acid phosphate) is liberated from the liver.[16] It is also known that such doses of histamine injected intravenously in dogs produce fatal shocks.[13,17] Therefore, preliminary to studies of anaphylaxis, a series of 8 dogs were injected intravenously with 4.5 mg of histamine acid phosphate per kilo. These animals were pretreated with a dose of Benadryl (10.0 mg

* This study was aided in part by a grant from the Clara A. Abbott Fund of Northwestern University Medical School.

The Benadryl used in these studies was furnished to us through the courtesy of Parke, Davis and Company.

1 Loew, E. R., Kaiser, M. E., and Moore, V., *J. Pharm. and Exp. Therap.*, 1945, **83**, 120.

2 Loew, E. R., and Kaiser, M. E., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 235.

3 Bartosch, R., Feldberg, W., and Nagle, E., *Pflüger's Arch.*, 1932, **230**, 129.

4 Wachstein, M., *Pflüger's Arch.*, 1932, **231**, 24.

5 Daly, I., Peat, S., and Schild, H., *Quart. J. Exp. Physiol.*, 1935, **25**, 32.

6 Ungar, G., and Parrott, J. L., *C. R. Soc. de biol.*, 1936, **123**, 676.

7 Ungar, G., Parrott, J. L., and Levillain, A., *C. R. Soc. de biol.*, 1937, **125**, 1015.

8 Schild, H. O., *J. Physiol.*, 1937, **90**, 34P.

9 Wells, J. A., and Morris, H. C., *Fed. Proc.*, 1945, **4**, 140.

10 Wells, J. A., Morris, H. C., Dragstedt, Carl A., and Bull, H. B., *J. Pharm. and Exp. Therap.*, in press.

11 Dragstedt, C. A., and Gebauer-Fuelnegg, E., *Am. J. Physiol.*, 1932, **102**, 512.

12 Gebauer-Fuelnegg, E., and Dragstedt, C. A., *Am. J. Physiol.*, 1932, **102**, 520.

13 Dragstedt, C. A., and Mead, F. B., *J. Pharm. and Exp. Therap.*, 1936, **57**, 419.

14 Code, C. F., *Am. J. Physiol.*, 1939, **127**, 78.

15 Dragstedt, C. A., and Mead, F. B., *J. Immunol* 1936, **30**, 319.

16 Ojers, G., Holmes, C. A., and Dragstedt, C. A *J. Pharm. and Exp. Therap.*, 1941, **73**, 33.

17 Dragstedt, C. A., and Mead, F. B., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1435.

TABLE I
Influence of Benadryl on Anaphylaxis in the Dog.

Degree of shock	No. and % of animals manifesting various degrees of shock			
	(26) Non-treated controls		(22) Benadryl (10 mg/kilo)	
	No.	%	No.	%
0	8	30.8	3	13.6
+	2	7.7	4	18.2
++	7	26.9	13	59.1
+++	0	0.0	2	9.0
++++	9	34.6	0	0.0

per kilo i. v.) which previous experience has shown to produce nearly maximum histamine antagonism. All of these animals had severe shocks, but none of them died. This experiment suggests that if histamine is the primary toxic factor in anaphylaxis, then no animals pretreated with 10.0 mg per kilo of Benadryl should die from anaphylaxis.

Forty-eight dogs were sensitized to horse serum by injecting 5 cc intravenously and 5.0 cc subcutaneously. From 13 to 15 days later these animals were anesthetized with sodium barbital and prepared for recording the carotid blood pressure. All animals were given a shocking dose of 10 cc of horse serum intravenously. In 22 of these animals, prior to the injection of horse serum, Benadryl (10 mg per kilo) was slowly injected intravenously.

The fall in blood pressure occurring as a consequence of anaphylaxis was roughly quantitated as follows: 0 = no fall in blood pressure, + = fall in blood pressure, but not to shock level (*i.e.* 35-45 mm. of mercury), ++ = fall in blood pressure to shock level, but with recovery beginning within 30 min., +++ = fall in blood pressure to shock level with no recovery within 30 min., ++++ = fall in blood pressure to shock level with death within 30 min.

Comparison of the 2 groups of animals (Table I) reveals that in contrast to a 34.6% mortality in the untreated series, no dogs died of anaphylaxis when they had been previously treated with 10 mg per kilo of Benadryl. It is apparent from the table that all evidence of anaphylactic vasodepression is not removed by Bernadryl. This is not surprising since we have shown that maximally effective doses of this drug do not completely abolish the actions of injected histamine in the dog. Therefore, assuming histamine to be the sole toxic factor in anaphylaxis in the dog, Benadryl would not be expected to completely abolish anaphylaxis.

It is not inconceivable that Benadryl modifies anaphylaxis in the dog by some action other than an antagonism of the histamine which is released. One obvious possibility is that it prevents the release of histamine. This possibility was investigated in the following way. Two dogs which had been previously sensitized to horse serum were shocked following the administration of 3.0 mg/kilo of Benadryl. At the point at which their respective blood pressures reached shock level a sample of their blood was drawn, heparinized and centrifuged. The serum from these dogs was then assayed by comparison with standard solutions of histamine acid phosphate on the blood pressure of the atropinized anesthetized cat. The outcome of the shock in the two animals was +++ and ++ respectively. The dog showing +++ shock was shown to have the equivalent of over 10 mcgm of histamine acid phosphate per cc of serum. The dog having ++ shock was shown to have the equivalent of 1 mcgm of histamine acid phosphate per cc of serum. These are amounts of histamine which are encountered in substantial anaphylactic shocks in the absence of Benadryl and indicate that Benadryl does not materially interfere with the release of histamine in anaphylactic shock in the dog.

Summary. The intravenous injection of Benadryl (10 mg per kilo) into horse serum sensitized dogs, prior to the reinjection of

horse serum, reduces the severity of anaphylactic shock in these animals, there being no deaths in 22 animals as against 9 deaths in 26 controls. As Benadryl has a similar modifying effect upon the shock induced by the injection of histamine, the results of these experiments are consistent with the theory that histamine plays a significant role in anaphylaxis in dogs. Unfortunately, Benadryl merely reduces, but does not obliterate, the vasodepressor effects of histamine and thus the present experiments with Benadryl do not permit conclusions as to whether histamine is or is not the sole vasodepressor factor in anaphylaxis in the dog.

15241

Corneal Reaction to Viruses of Equine Encephalomyelitis After Intra-Ocular Injection.*

C. A. EVANS AND V. S. BOLIN.

From the Department of Bacteriology and Immunology, School of Medicine, University of Minnesota.

In a previous publication[1] it was reported that injection of certain viruses into the eyes of suitable animals caused specific reactions in the ocular tissues. Corneal edema and opacity were produced when the viruses of fox encephalitis, influenza, and equine encephalomyelitis were employed. It was demonstrated that virus of fox encephalitis, even in minute dosage, would infect the corneal endothelium and induce the corneal reaction in dogs, foxes and raccoons.[2,3] The influenza virus caused an entirely similar reaction in the eyes of rabbits in spite of a complete absence of infection, by a direct toxic effect.[4] The virus did not grow in the rabbit eye and was effective only in very large doses.

Further studies reported in this paper suggest that the corneal opacity in rabbits caused by the viruses of western and eastern equine encephalomyelitis is analogous to the toxic reaction demonstrated for influenza virus even though these viruses may grow to a limited extent in the ocular tissues.

In our first experiment a 10^{-3} dilution of mouse brain infected with a highly virulent strain of virus of W.E.E. (Western Equine Encephalomyelitis) was injected into the anterior chamber of one eye of each of 3 rabbits. At 48 hours all showed some cloudiness of the cornea and at 3 days the corneas of all injected eyes were opaque.

In subsequent experiments 27 rabbits have been injected with 2 different strains of western virus. One of the western strains was highly virulent and had been maintained by passage in mice for many years by Dr. Carl M. Eklund, who obtained it from Dr. P. K. Olitsky of the Rockefeller Institute for Medical Research. This we call the Rockefeller strain. The second strain of western virus had been isolated from a fatal human case of encephalitis by injection of brain tissue into guinea pigs. Some of the infected guinea pig brain tissue that had been kept frozen for more than a year was used to infect guinea pigs and mice, the brains of which served as the source of virus for injection into eyes. This is called the "low passage" strain of virus.

* Aided by grants from the John and Mary R. Markle Foundation and the Graduate School of the University of Minnesota.

[1] Evans, C. A., Yanamura, H. Y., and Green, R. G., *Science*, 1943, **98**, 45.

[2] Evans, C. A., Yanamura, H. Y., and Green, R. G., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 183.

[3] Green, R. G., Evans, C. A., and Yanamura, H. Y., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 186.

[4] Evans, C. A., and Rickard, E. R., PROC. SOC. EXP. BIOL. AND MED., 1945, **58**, 73.